American Journal of Medical Genetics 70:427–436 (1997)

Long-Term Survival in Typical Thanatophoric Dysplasia Type 1

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Thanatophoric dysplasia (TD), a severe skeletal dysplasia, is virtually always lethal neonatally, although a few previous reports have documented survival up to 4.75 years. We present a patient with survival beyond age 9 years and summarize his growth, development and medical history. The common Arg248Cys mutation in the extracellular region of fibroblast growth factor receptor 3 (FGFR3) was identified, eliminating the possibility that his long-term survival is attributable to an atypical mutation. This patient (and at least one other TD long-term survivor) have a rare skin disorder, acanthosis nigricans, which also occurs in Crouzon syndrome when caused by a FGFR3 mutation. Therefore, any molecular model of the origin of acanthosis nigricans secondary to FGFR3 mutations must account for the association of diverse mutations and these cutaneous effects. Am. J. Med. Genet. 70:427–436, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: thanatophoric dysplasia; fibroblast growth factor receptor 3 (FGFR3); bone dysplasias; acanthosis nigricans; lethality; unexpected survival; craniosynostosis

INTRODUCTION

Thanatophoric dysplasia was originally described by Maroteaux et al. [1967], who coined the term "thanatophoric," meaning "death bearing" in Greek. At the time of this designation, death, typically due to respiratory failure, occurred invariably within the first few hours or days of birth. TD is characterized by marked rhizomelic shortness of the limbs with skin redundancy, a narrow thorax with short ribs, markedly flattened vertebral bodies, a short pelvis, a relatively large head with frontal bossing, prominent eyes, hypertelorism, and depressed nasal bridge. In some cases, premature closure of cranial sutures results in *Kleeblattschädel* or cloverleaf skull. Two major forms of TD have been characterized: TD type 1 (TD1) with curved femora and very flat vertebral bodies and TD type 2 (TD2) with straight femora and taller vertebral bodies [Langer et al., 1987; Spranger and Maroteaux, 1990]. Very few TD1 cases have a cloverleaf skull while most TD2 cases have severe craniosynostosis [Langer et al., 1987; Spranger and Maroteaux 1990].

Recently, a few children with TD and longer survival have been documented. Stensvold et al. [1986] reported a 169 day survival, Tonoki [1987] reported a 212 day survival, and MacDonald et al. [1989] reported 4.75 years and 4.0 years survivals. In these long-term survivors, respiratory insufficiency arose secondary either to reduced chest circumference and/or lower brain stem compression resulting from a diminutive foramen magnum. Additional central nervous system abnormalities have included hydrocephalus, polymicrogyria, neuronal heterotopia, megalencephaly, cerebral gyral disorganization, hippocampal malformation, nuclear dysplasia, abnormal axonal bundles, and cerebellar hypoplasia in a small posterior fossa [Ho et al., 1984; Shigematsu et al., 1985]. Other complications noted in the natural histories described by MacDonald et al. [1989] included seizures and hearing loss.

We describe the growth, development and medical history of a patient with TD1 who is still living at age 9 years.

CLINICAL REPORT

The male patient, now 9.0 years, was delivered by cesarean section at approximately 36 weeks gestation to a 27-year-old gravida 3 para 2 mother and 35-year-old father. Markedly decreased intrauterine movement and polyhydramnios were noted during pregnancy. Prenatal ultrasound study suggested breech position.

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Received 29 August 1996; Accepted 15 December 1996

Apgar scores were 2, 5, and 6 at 1, 5, and 10 minutes, respectively. Birthweight was 3.26 kg [50th centile (compared with normal standards)], birthlength was 41 cm [–4.0 standard deviations (SD) (compared with achondroplasia standards)], and birth occipito-frontal head circumference (OFC) was 39.5 cm [55th centile (compared with achondroplasia standards)]. Frontal bossing, flat facies, micromelia, and small chest were noted at birth. Intubation was performed at approximately 1 minute of age due to absence of spontaneous respirations. Within the first few hours of life, he was transferred to an intensive care unit and, following clinical examination and review of radiographs (which showed typical signs of TD1, Fig. 1), a diagnosis of thanatophoric dysplasia was made. He was hospitalized for 18 m following his birth and then discharged to home care.

Linear growth (Fig. 2, top left) has been exceedingly slow, in the range of –6 to –6.5 SD compared to achondroplasia standards, yielding an estimated adult height of 85 cm. Ponderal growth (Fig. 2, bottom left) has exceeded linear growth and may contribute to the patient's gross motor delays. Body disproportion has persisted, with marked rhizomelic shortness and very little growth of the limbs (Fig. 3). OFC has decreased from greater than +1 SD in infancy to –1.7 SD at 8.7 years when compared to children with achondroplasia (Fig. 2, top right). Craniofacial manifestations also have persisted (Fig. 4).

Serial neuroimaging has shown mild ventriculomegaly, stable since age 9 months, synostosis of the coronal and lambdoidal sutures, first noted at 3 years, and marked basicranial and upper cervical stenosis. The foramen magnum is small and particularly narrowed transversely (Fig. 5) with very modest growth at about –1.5 SD when compared with achondroplasia standards (Table I). Craniocervical decompression was considered at 4.2 years but rejected since frank brainstem and cervical cord compression was not present. Nonetheless, some neurologic signs suggest the presence of a high cervical myelopathy: increased leg reflexes, sustained ankle clonus, and bilateral upgoing Babinski sign. Central respiratory regulation appears to be maintained, although unexplained episodes of bradycardia have been observed. Seizures were first noted at 7 months. At age 9 years, weaning from antiseizure medication was unsuccessful, resulting in recurrence of generalized seizure activity. Seizures are currently controlled with carbamazepine.

Fig. 1. Newborn "babygram" demonstrating typical findings of TD1, including profound platyspondyly, decreased thoracic volume, characteristic pelvic configuration, long bone shortness, and femoral bowing (so-called "telephone receiver" femurs).

As with growth, development has been consistently and severely delayed. Although accurate assessment is impossible, general cognitive ability at 8 years was at an approximately 18 months level. At 4.8 years, language skills assessments did not exceed 17 months levels. At age 9 years, the patient vocalized but had no distinct words. External factors such as tracheostomy-dependent ventilation, long-term hospitalization, and hearing loss, as well as primary central nervous system factors may have contributed to his language delays. Motor skills at 4.8 years fell within the 2 to 12 months range. Currently, he is able to roll, scoot, sit unsupported, and pull to stand with assistance. He feeds himself, uses some switch plates/latches, uses a manual wheelchair for mobility, attends a class for severely multiply impaired children, and receives occupational, physical, speech, and hearing therapy.

Respiratory difficulties have persisted throughout the patient's life. Chest remains small (Fig. 2 bottom right). Tracheostomy was performed at 8 months of age. He has remained ventilator dependent. At 9 years, 10–12 minutes of independent breathing with supplementary oxygen was tolerated. He has survived multiple airway infections including one with respiratory syncytial virus.

Recurrent otitis media led to myringotomy and tube placement at 2.3 years. Auditory evoked potential at 3.3 years suggested mild to possibly moderate bilateral hearing loss. Bilateral hearing aids are used.

Other concerns have included the following. Multiple renal calculi have been observed. Gastrostomy was placed at 1.6 years of age but currently is used only for medication and during illness. Upper lumbar kyphosis has been present since 2.3 years and has been persistent but not progressive. Generalized joint hypermobility as well as hip and knee flexion contractures have been noted.

Thickening of the skin of the neck, axillae, tracheostomy site, and overlying the base of the coccyx was first noted in 1990, and a dermatologic diagnosis of acanthosis nigricans was made in 1993. At 9 years, severely thickened skin on the face, forehead, neck, and around the site of the gastrostomy was present (Fig. 6).

Radiologic changes are documented in Figure 1 and

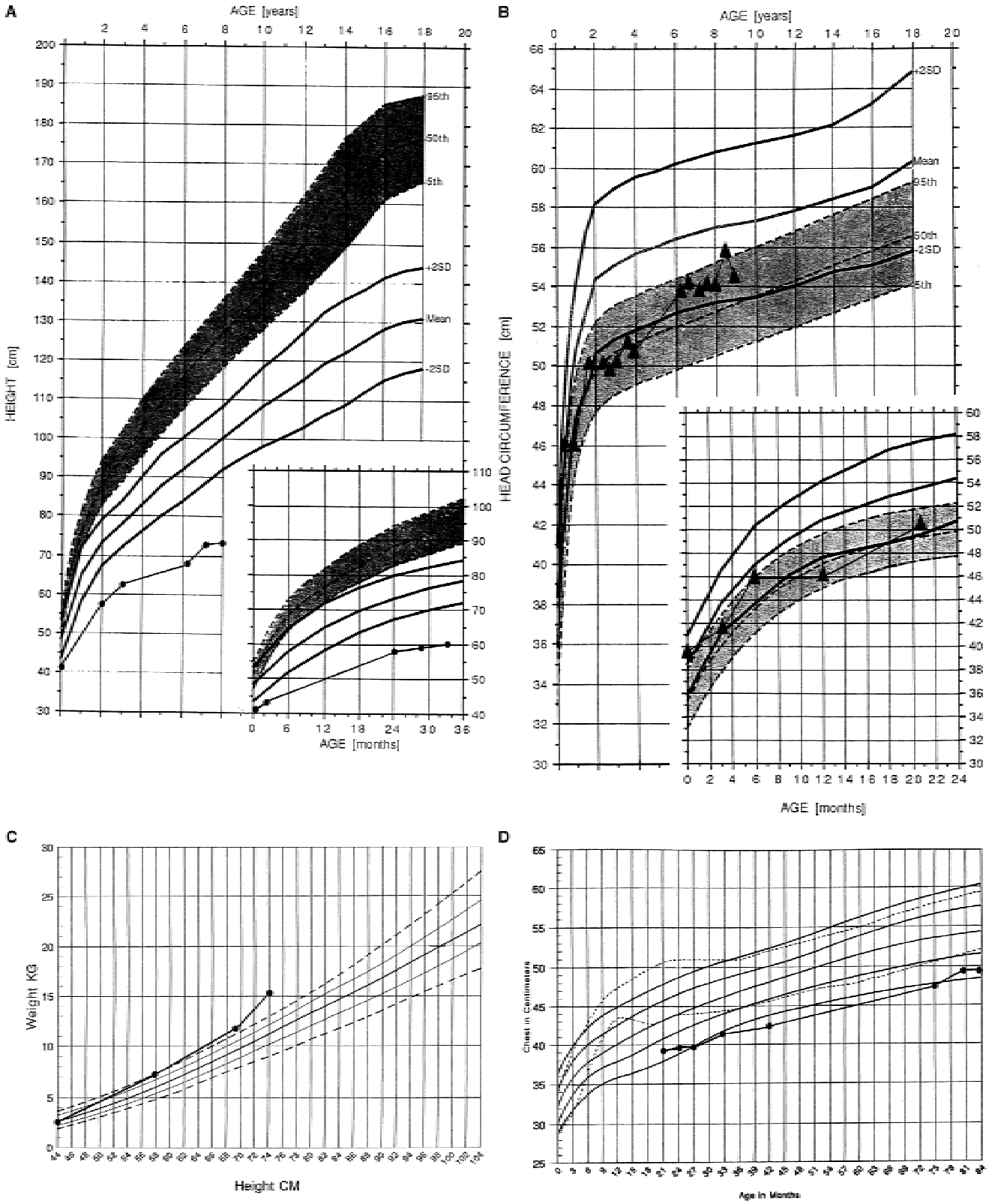

Fig. 2. Plots of linear growth (**A**), occipito-frontal circumference (**B**), weight by length (**C**), and chest circumference (**D**). Linear growth has been maintained between −6 and −7 SD below the mean for children with achondroplasia. Relative obesity has developed. Head circumference has decreased from above +1 SD in early infancy to about −1.7 SD (when compared with children with achondroplasia). Most chest circumference measures are at about 2 SD below the mean for achondroplasia, indicative of chest constriction of greater severity than is routinely seen in heterozygous achondroplasia. Data are plotted with respect to graphs initially published in Horton et al., 1969 (A and B), Hunter et al., 1996a (C), and Hunter et al., 1996b (D).

Fig. 3. Full body photographs at 3 years (**left**) and 9 years (**right**) showing marked limb shortness and thoracic narrowing.

Figures 7–11. Newborn radiographs (Fig. 1) show signs identical to those thought to be typical for TD1 [Langer et al., 1987] including profound platyspondyly, short ribs, horizontally flattened ilia, narrow sacrosciatic notch, and markedly short long bones with considerable metaphyseal widening. With time, the chest has grown (Fig. 7) but still demonstrates considerable constriction and rib shortness. The spine (Fig. 8) shows remarkable maturation and ossification so that at older ages the characteristic severe platyspondyly has disappeared and the spine has assumed an appearance rather similar to that anticipated in children with achondroplasia. In addition, there has been development of a thoracolumbar kyphosis. All long bones (Figs. 9, 10) show marked metaphyseal flare and shortness with remarkably little change in character with increasing age. Metacarpals, metatarsals, and phalanges remain profoundly short with extreme delays in maturation (Fig. 11). Overall, while the spine has assumed characteristics similar to achondroplasia, the long bones and pelvis remain virtually identical in features to those seen in infancy.

MOLECULAR STUDIES

Molecular studies were carried out on peripheral blood samples by the Department of Biological Chemistry and Human Genome Research Center at the University of California-Irvine (John J. Wasmuth, Ph.D.). The common TD1 Arg248Cys mutation in the extracellular region of the fibroblast growth factor receptor 3 (FGFR3) gene was identified.

DISCUSSION

Thanatophoric dysplasia results from dominant new mutations and is thought to have an incidence of approximately one in 37,000 live births [Martínez-Frías et al., 1988], although many clinicians suspect that its true incidence is greater.

Survival in TD1

In most infants with TD1, death is thought to arise secondary to chest constriction and consequent respiratory insufficiency, or to foramen magnum stenosis and resultant failure of respiratory control. It has been suggested that limitation of intervention is appropriate because of the inevitable lethal nature of TD [Jones, 1988]. Aggressive neonatal management has, at times, not even resulted in short-term survival. However, some infants with TD1 clearly can survive. This report

Fig. 4. Facial appearance at age 9 years.

of survival beyond 9 years in a child with a typical TD1 mutation means that survival is not because of mutational heterogeneity. Unanticipated long-term survival raises issues regarding what intensity of medical care is reasonable. Decision making depends, in part, on an understanding of expectations for those who may become long-term survivors.

Natural History of TD1

In a typically lethal disorder such as thanatophoric dysplasia, it is necessary to provide appropriate and knowledgeable counseling where survivability is unlikely but conceivable. For such counseling, the growth, development and medical history of even just one child's 9-year survival is particularly enlightening.

Growth potential is markedly limited. Indeed, on the basis of the rate of growth seen in the reported patient, one can anticipate ultimate adult stature in the range of 80–90 cm (32–35 inches).

Cognitive development has been markedly delayed. It is impossible to determine the contributions of the many factors which may effect such delays. They may, in part, be intrinsic to the effects of the TD1 mutation. Indeed, since FGFR3 is highly expressed in the central nervous system [Peters et al., 1993] one might anticipate that mutations could result in structural or functional brain abnormalities. None of the previously reported structural aberrations [Ho et al., 1984; Shigematsu et al., 1985] were seen in sequential neuroimaging of the patient reported here. Sequelae such as high cervical myelopathy secondary to craniocervical spinal stenosis may have marked effects on potential ambulation. It is likely that some of the motor abnormalities seen in this patient are attributable to this. Motoric delays also are exacerbated by biophysical factors such as limb shortness, brachydactyly, hip and knee flexion contractures, and medical equipment limitations. Long-term medical care and chronic ventilator dependence may impede normal cognitive and emotional growth.

Home care has been possible and successful but has required extensive health maintenance measures on the part of caregivers (including relatives and home nursing personnel). Families need to anticipate frequent medical exacerbations requiring recurrent hospitalizations. Likewise, the possibility of a lethal complication remains an ever present concern. Although there are severe delays in development, productive relationships between family and friends have been formed. Special education programs can be designed to conform with the needs and limitations of such children.

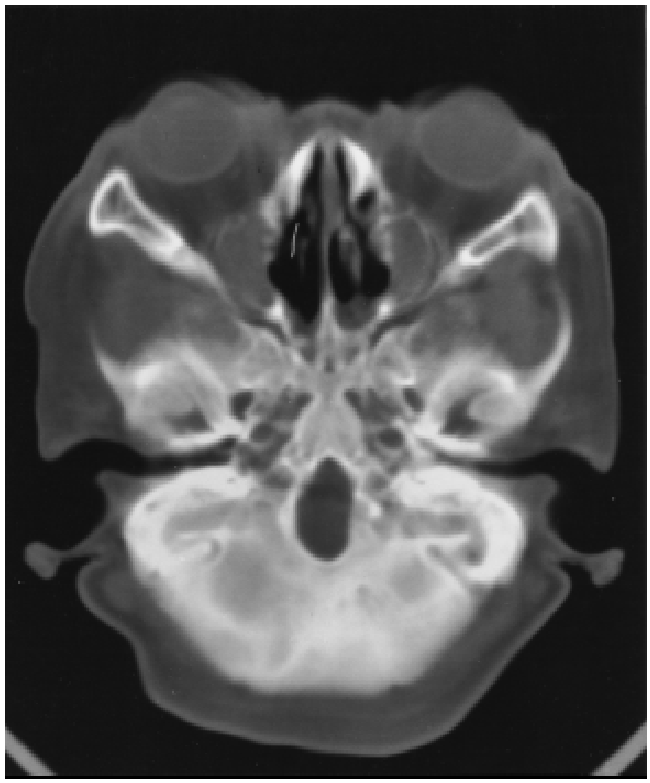

Fig. 5. Computerized tomography at 8 years of age. Note the constricted foramen magnum which is particularly narrowed in the transverse plane.

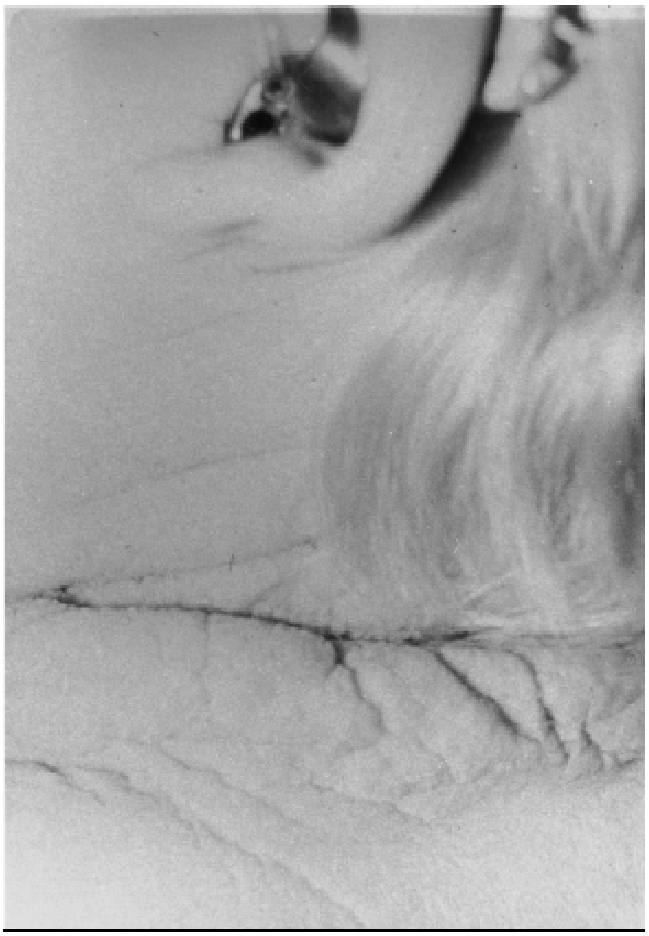

Fig. 6. Acanthosis nigricans of the neck.

Major medical issues have included respiratory insufficiency and neurologic abnormalities.

The patient reported here remains ventilator dependent. Although there has been modest success in early stages of ventilator weaning, it is likely that complete or partial ventilator dependence will continue. Likewise, need for a tracheostomy (to decrease airway dead space and because of ventilator dependence) is likely permanent. Multiple etiologies have been suggested for the respiratory insufficiency in thanatophoric dysplasia: pulmonary hypoplasia secondary to reduced thoracic growth [Harding et al., 1990] and lower brainstem compression resulting in disorders of respiratory control caused by foramen magnum stenosis [Pauli et al., 1984]. In at least one TD case, foramen magnum stenosis has been specifically implicated as leading to impaired diaphragmatic function and ventilation [Faye-Petersen and Knisely, 1991]. It is likely that both diminished chest size and foramen magnum stenosis have contributed to our patient's respiratory insufficiency. In TD and other similar disorders, there have been a few treatments proposed to either increase thoracic dimensions or reduce cervical compression. For example, in Jeune syndrome, surgical thoracic expansion has been of limited benefit [Todd et al., 1986]. Suboccipital craniectomy in homozygous achondroplasia has been found to relieve respiratory complications [Hecht et al., 1986], whereas in one individual with TD, brainstem decompression resulted in only temporary ventilator independence [MacDonald et al., 1989].

Neurologic abnormalities in the patient reported here have included hyperreflexia and clonus and a recurrent seizure disorder. The former is likely to be secondary to subtle cervical myelopathic changes. The cause of the seizure disorder remains unknown. Seizures have been relatively easily controlled. Mixed

TABLE I. Foramen Magnum Measurements From 9 Months to 8.4 Years of Age[a]

Transverse diameter	Achondroplasia	Normal
9 months: 11.1 mm	−1.25 SD	−5.43 SD
40 months: 11.6 mm	−1.50 SD	−6.57 SD
75 months: 11.8 mm	−1.75 SD	−6.86 SD
86 months: 13.2 mm	−1.50 SD	−6.57 SD
101 months: 13.2 mm	−1.50 SD	−6.57 SD
Sagittal diameter	**Achondroplasia**	**Normal**
9 months: 11.2 mm	−1.67 SD	−2.40 SD
40 months: 20.2 mm	−1.20 SD	−2.67 SD
75 months: 22.4 mm	−1.20 SD	−2.60 SD
86 months: 23.7 mm	−1.07 SD	−2.89 SD
101 months: 23.7 mm	−1.14 SD	−2.89 SD

[a]Shown are SD from the mean for the CT derived measures when compared with normal and achondroplastic standards [Hecht et al., 1989].

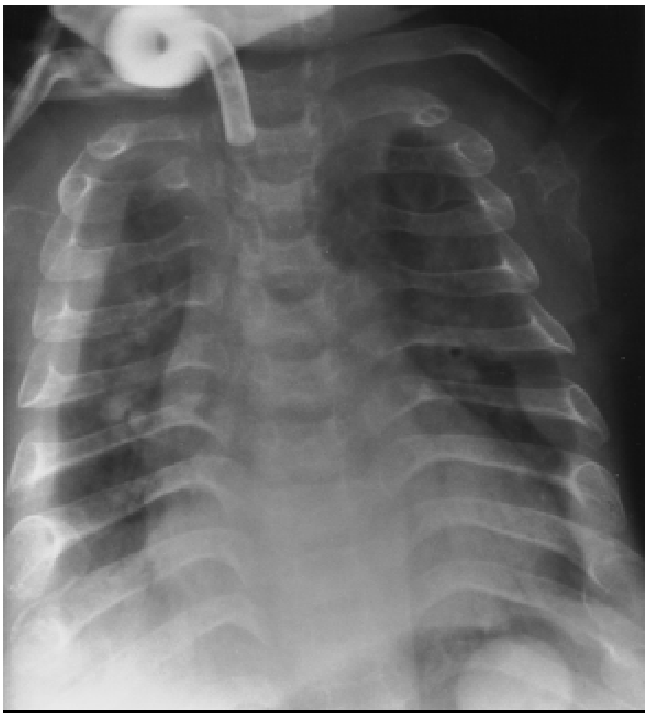

Fig. 7. Chest radiograph at 2.9 years. There has been only modest growth of the thorax since birth. Ribs are considerably thicker but remain foreshortened.

hearing loss may arise, as in the patient reported here, secondary to recurrent middle ear disease and, perhaps, because of primary neural anomalies or bony abnormalities related to FGFR3 function.

Multiple suture synostosis was identified at about 3 years of age. Other FGFR3 mutations (including those causing Crouzon-acanthosis nigricans and TD2) are associated with craniosynostosis [Meyers et al., 1995; Langer et al., 1987]. Its infrequency in reports of TD1 is probably because of later onset and more modest severity in a population of infants most of whom do not survive long enough to express this feature.

In addition to the patient reported here, two other children with TD (presumably type 1) received aggressive perinatal and long-term care and have lived to 9 years (Scott, unpublished data) and 10 years (Hunter, unpublished data). One boy, 9 years, was intubated immediately following birth and has been ventilated long-term. Home health care was initiated after 7 months of hospitalization. Medical history includes multiple infections, hydrocephalus, hearing loss, and the appearance of acanthosis nigricans at least by age 5.7 years. Development is severely delayed, but some signing and self-help skills have emerged (Scott, unpublished data). A second child, female and now approximately 10 years, was previously reported [MacDonald et al., 1989]. Ventilatory support was not required until age 2 months, but, despite cervical decompression, nearly continuous ventilation has been needed since. Currently, she is in long-term hospitalization (Hunter, unpublished data).

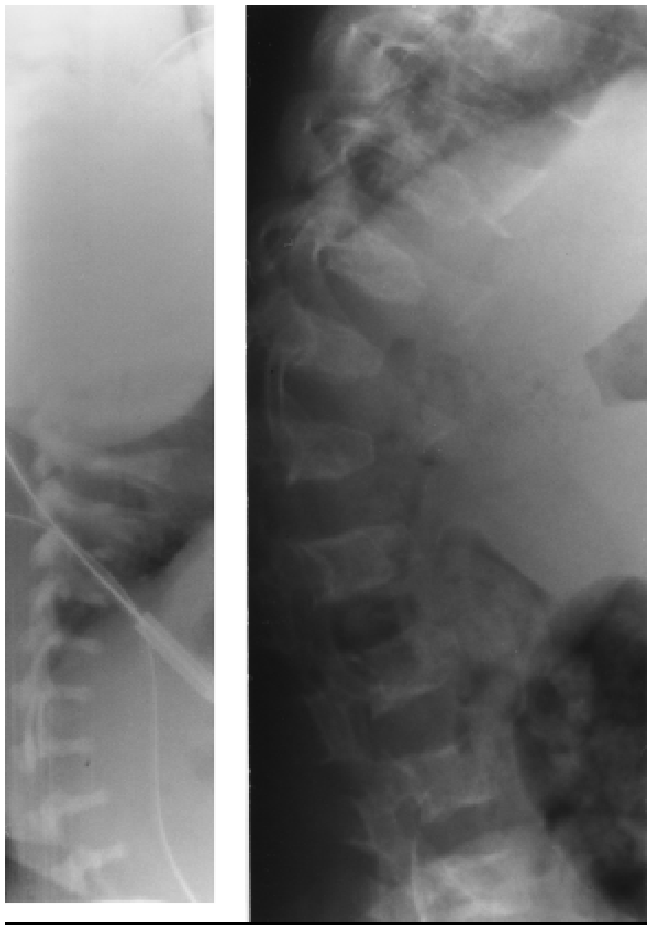

Fig. 8. Lateral spine radiographs, at birth (**left**) and 7.2 years (**right**).

Issues of Decision Making in "Lethal" Disorders

Issues related to actions that may prolong survival are not limited to TD. Other disorders thought to be universally lethal have also yielded long-term survivors. Children with typically lethal homozygous achondroplasia have lived beyond infancy suggesting that aggressive treatment such as oxygen supplementation, ventriculoperitoneal shunting, and suboccipital decompression may increase life expectancy [Pauli et al., 1983]. A 4-year-old child [Stern et al., 1990] as well as an adult (Pauli, unpublished data) are known to be affected with atelosteogenesis type III. Other disorders in which variable lifespans are already recognized, are now resulting in more long-term survivors. For example, in rhizomelic chondrodysplasia punctata (RCP), survival into childhood and young adulthood was described recently [Wardinsky et al., 1990; Holland et al., 1996]. Likewise, in Jeune syndrome, there have been occasional reports of survival into adulthood [Giorgi et al., 1990]. Conversely, there are subsets of less severe diseases which are only rarely life-threatening. For example, while mild or moderate respiratory distress is common, most children with spondyloepiphyseal dysplasia congenita do not die of respiratory difficulties. Nevertheless, there have been a few reports of deaths due to respiratory complications [Macpherson and Wood, 1980; Harding et al., 1990].

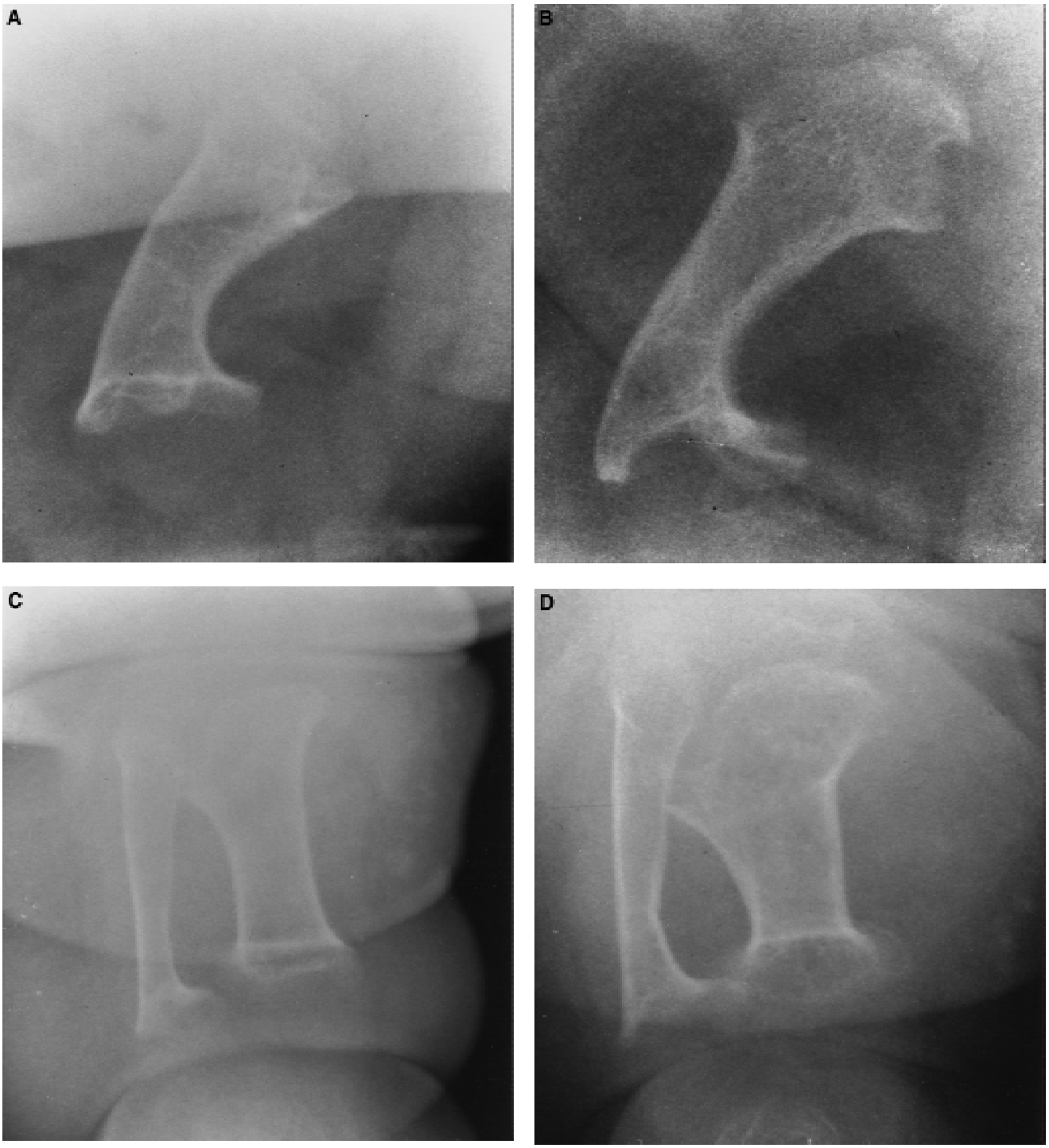

Fig. 9. Femur radiographs at 2.3 years (**A**) and 7.2 years (**B**) and tibia/fibula radiographs at 2.3 years (**C**) and 7.2 years (**D**).

For most potentially lethal bone dysplasias, risks of death have shared bases. Most often, death is caused by respiratory failure resulting from some combination of centrally-mediated apnea, airway incompetence and severe chest constriction. Given the similar pathogenetic mechanisms and given reports of long-term survivors for most disorders, treatment decisions cannot be made based on etiologic diagnosis alone. This forces a reevaluation of the designation of a disorder as "lethal." What determines that a disorder is lethal? In light of the possibility for survival, should economic considerations play a role in decision making? How should expectant parents be counseled regarding prognosis, particularly as prenatal diagnosis becomes more available and, on the basis of molecular delineation, more precise?

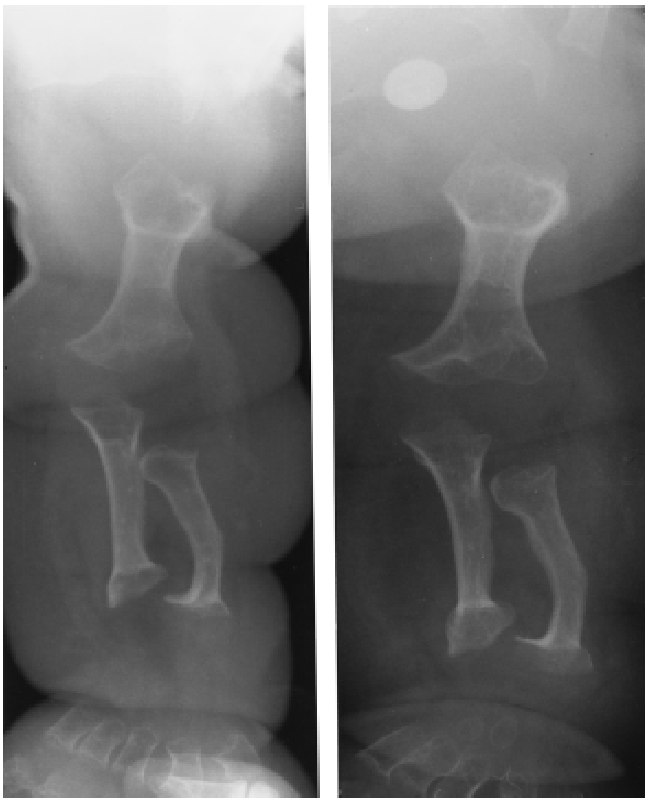

Fig. 10. Arm radiographs at 3.3 years (**left**) and 7.2 years (**right**).

FGFR3 Mutations and Acanthosis Nigricans

Specific mutations in fibroblast FGFR3 have been identified in TD [Tavormina et al., 1995; Rousseau et al., 1995]. Furthermore, an Ala391Glu mutation in the transmembrane region of FGFR3 (rather than the more typical FGFR2 mutations for most forms of Crouzon syndrome) has been identified in patients with Crouzon syndrome who have acanthosis nigricans. Acanthosis nigricans is also present in the patient reported here and in at least one other long-term survivor with TD. Although co-occurrence of acanthosis nigricans and Crouzon syndrome has been reported several times [Meyers et al., 1995], TD plus acanthosis nigricans has not been described previously. However, the absence of such reports is most likely because long-term survival in TD is rare and acanthosis nigricans typically does not develop until after infancy. Curiously, a half century ago, the cosegregation of acanthosis nigricans and an achondroplastic-like dwarfing process was described [Lange, 1938]; one might posit that this family might also have had yet another FGFR3 mutation. Other FGFR3 mutations which result both in skeletal dysplasia and acanthosis nigricans may yet be discovered. Any molecular postulate used to explain how acanthosis nigricans arises secondary to FGFR3 mutations [Meyers et al., 1995] must take into account its occurrence in both Crouzon syndrome and TD1.

ACKNOWLEDGMENTS

We recognize the gracious assistance of the family of the patient. We are also grateful to the late John Wasmuth, Ph.D. and to Patricia Tavormina, Ph.D. at the University of California-Irvine for their laboratory expertise. The unpublished information provided by Dr. Charles Scott and Dr. Alasdair Hunter have enriched this manuscript and significantly added to the body of knowledge regarding long-term survival in thanatophoric dysplasia. V. Kim Horton, RN, MS is especially thanked for help with this project.

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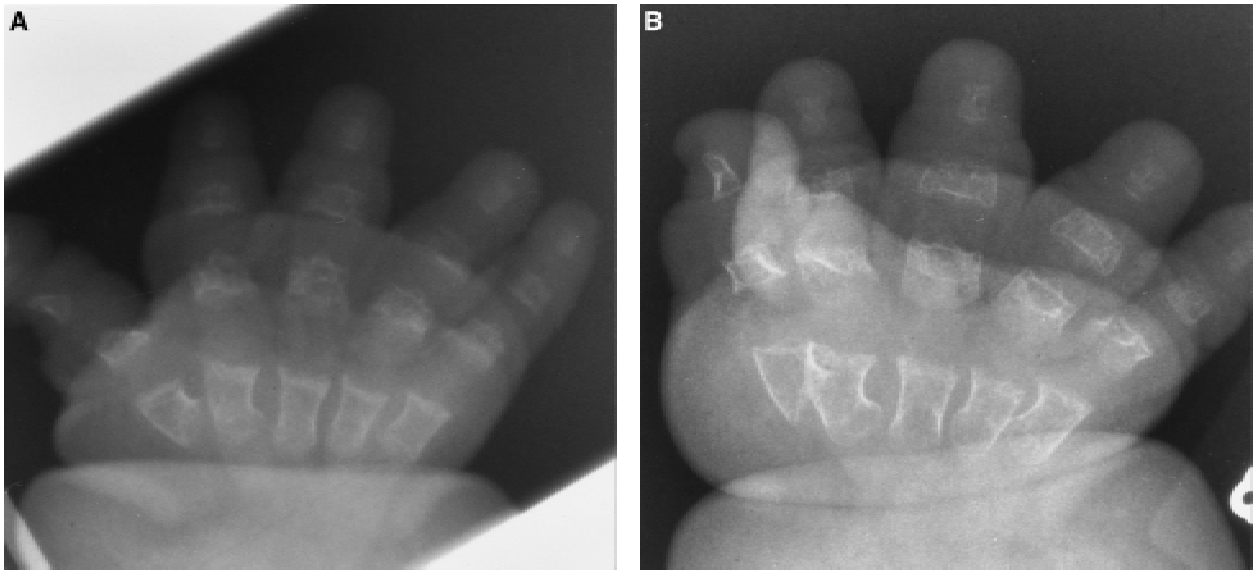

Fig. 11. Hand radiographs at 6 months (**A**) and 3.3 years (**B**).

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